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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,282	06/18/2001	Bonnie M Davis	U013469-7	6731

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/856,282	DAVIS, BONNIE M	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,10-20,24-26 and 29-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,10-20,24-26 and 29-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/6/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-5, 10-20, 24-26, and 29-42 are presented for examination

Applicants' response and amendments to the claims, filed 7/6/2009, are acknowledged and entered. Claim 21 has been cancelled by Applicant. Claims 1, 3-5, 10-20, 24-26, and 29-42 are pending and under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/6/2009 has been entered.

Response to Arguments

Any previous rejections and/or objections to claim 21 are withdrawn as being moot in light of Applicant's cancellation of the claim.

Applicants' arguments have been fully and carefully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The instant claims recite dosage forms comprising a centrally-acting acetylcholinesterase inhibitor (*e.g.*, galanthamine) formulated so as to delay the activity of the acetylcholinesterase inhibitor for a predetermined period of from four to twelve hours.

Claims 1, 3-5, and 10-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** (Published Nov. 17, 1988) in view of **Conte *et al.*** (Biomaterials, 1993, vol. 14, no. 13, pages 1017-1023) and **Davis** (USP No. 5,585,375; Issued Dec. 17, 1996).

WO 88/08708 teaches compounds of formula (I) for use in the treatment of Alzheimer's disease (Abstract). Such compounds are galanthamine-analogues as recited in claims 1, 3-5, and 10-19 (pages 9-17). The compounds of the invention are taught to be inhibitors of acetylcholinesterase (page 38). Compositions for administration to patients having Alzheimer's disease, including sustained release delivery formulations, are taught at page 24, first and second paragraph. With respect to the claimed half life of from one to eleven hours as recited in the instant claims, the half life of any compound is a property of that compound and thus not separable from the compound itself. Therefore, because WO 88/08708 teaches the claimed compounds, the properties of these compounds that Applicants recite in the instant claims are necessarily present. WO 88/08708 does not teach a formulation wherein acetylcholinesterase inhibition is avoided for a predetermined period of from four to twelve hours as recited in the instant claims.

However, Conte *et al.* teach methods of formulating pharmaceutical active agents in press-coated tablets for time-programmed release of drugs (Abstract). The delay in release start is taught to not be influenced by the core composition and depends only on the shell formulation (*id.*). Suitable drugs for such time-programmed release include active agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity (*e.g.*, psychotropic active drugs) (page 1017, left column, second full paragraph). The press-coated tablets taught in Conte *et al.* release drugs at a specific rate, but the release starts only after a well defined period of time (page 1017, right column, first full paragraph). With respect to the delay periods recited in claims 1 and 3-4 (i.e., 4 to 12 hours, 6 to 9 hours, or 8 to 12 hours), Conte *et al.* teach such delay periods, *e.g.*, 240 minutes, 480 minutes, and 720 minutes (Figures 6, 7, and 8).

Davis is provided as evidence that acetylcholine levels in the brain are known to be higher in animals that are awake than those that are sleeping and that chemicals that that interfere with cholinesterase mechanisms are known to promote REM sleep over slow wave sleep (col. 1, lines 10-22). Thus, acetylcholine levels clearly depend on physiological and/or physiopathological changes of circadian rhythmicity.

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a acetylcholinesterase inhibitor such galanthamine or galanthamine-analogues as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease. The skilled artisan would have been motivated to do so because Conte *et al*. teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity (as also evidenced by Davis) and thus suitable for incorporation into the press-coated tablets taught therein. In this regard, it is noted that WO 88/08708 teaches that galanthamine was known in the art as an agent useful in treating Alzheimer's disease "and related dementias" (page 1) and inhibits acetylcholinesterase (page 38), a reasonable interpretation of which is that galanthamine is a psychotropic drug and thus reasonably suggested by Conte *et al*.[1] Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of acetylcholinesterase inhibitor medication while they are sleeping because acetylcholine levels are lower than when the patient is awake. In other words, because acetylcholinesterase is an enzyme that "breaks down" acetylcholine, since acetylcholine levels are already low during the night, there would no need to inhibit the break down of already low levels of acetylcholine. As such, Conte *et al*. provides methods of formulating compositions that will aid in patient compliance, *i.e*., a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

[1] A psychotropic drug, as understood by those skilled in the art, is a chemical substance that acts primarily upon the central nervous system where it alters brain function.

Claims 1, 3-5, and 20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Conte *et al***. in view of **Davis** and **Nordberg *et al.*** (Drug Safety, 1998, vol. 19, no. 6, pages 465-480).

Conte *et al*. and Davis teach as discussed *supra*. The references does not teach the acetylcholinesterase inhibitor, rivastigmine, as specifically recited in claim 20.

However, Nordberg *et al*. compare the tolerability and pharmacology of cholinesterase inhibitors in the treatment of Alzheimer's disease. In this regard, the reference teaches that cholinesterase inhibitors are currently the most established treatment strategy in Alzheimer's disease and that three cholinesterase inhibitors are in clinical use: tacrine, donepezil, and rivastigmine (Abstract). Further, Nordberg *et al*. teach that other cholinesterase inhibitors such as galanthamine (also recited in the instant claims) are under clinical evaluation (*id*.).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate rivastigmine as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease. The skilled artisan would have been motivated to do so because Conte *et al*. teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity (as evidenced by Davis) and thus suitable for incorporation into the press-coated tablets taught therein. In this regard, it is noted that Nordberg *et al*. teach that rivastigmine inhibits acetylcholinesterase and was known in the art as an agent useful in treating Alzheimer's disease (Abstract; pages 475-476), a reasonable interpretation of which is that rivastigmine is a psychotropic drug and thus reasonably suggested by Conte *et al*.[2] Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's dementia or behavioral abnormalities would not be in need of medication while they are sleeping because acetylcholine levels would be lower than when the patient is awake. As such, Conte *et al*. provides methods of formulating compositions that will also aid in patient compliance, *i.e*., a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake

[2] A psychotropic drug, as understood by those skilled in the art, is a chemical substance that acts primarily upon the central nervous system where it alters brain function.

because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708**, **Conte *et al.***, and **Davis** as applied to claims 1, 3-5, and 10-19 above, and further in view of **Faber *et al.*** (Am. J. Psychiatry, Jan. 1999, vol. 156, no. 1, page 156).

WO 88/08708, Conte *et al.*, and Davis teach as discussed *supra*. The references do not teach the administering of a compound (*e.g.*, Probanthine) that reduces the peripheral effects of the claimed acetylcholinesterase inhibitors.

However, Faber *et al.* teach that propantheline[3], a peripherally acting anticholinergic medication, reduces the peripheral cholinergic activity caused by administration of the cholinesterase inhibititor tacrine (page 156, left column). Based on the results of their study, the authors suggest the use of adjunctive propantheline in patients with cholinergic effects from tacrine or other cholinesterase inhibitors.

Accordingly, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer acetylcholinesterase inhibitors as recited in the instant claims in conjunction with a compound that reduces its peripheral effects, such as propantheline as motivated and suggested by Faber *et al.*

Claims 24-26 and 29-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708**, **Conte *et al.***, and **Davis** as applied to claims 1, 3-5, and 10-19 above, and further in view of **Riemann et al.** (Psychiatry Research, 1994, vol. 51, pages 253-267).

WO 88/08708, Conte *et al.*, and Davis teach as discussed *supra*. The references do not explicitly teach the administering of the formulations suggested therein so as to avoid release of the acetylcholinesterase inhibitor for the next anticipated sleep time (claim 41) or to allow a patient's central nervous system to become hypocholinergic during the period of desired sleep so as to avoid sleep disturbances during hours of desired sleep (claim 42).

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[3] Propantheline is the common chemical name of the drug sold as Pro-Banthine.

However, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of medication while they are sleeping because acetylcholine levels would be expected to be lower than when the patient is awake as evidenced by Davis. As such, Conte *et al.* provides methods of formulating compositions that will aid in patient compliance, *i.e.*, a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up, when acetylcholine levels are expected to rise. Riemann et al. teaches that galanthamine is used to treat Alzheimer's disease (page 254). In addition, Riemann et al. disclose that galanthamine increases the time awake and the number of awakenings in healthy patient compared to patients not receiving galanthamine (Table 3). Here, the skilled artisan is provided with the necessary motivation to develop controlled release formulations of galanthamine (such as those suggested and motivated by WO '708 in view of Conte *et al.*) in order to avoid waking a patient from sleep.

Accordingly, the skilled artisan would have been imbued with at least a reasonable expectation that delaying the release of galanthamine or analogues thereof during periods of sleep would avoid waking a patient from sleep since no anticholinesterase inhibition would occur. In support of this argument, the Examiner refers to Applicant's disclosure that it was known in the art at the time the invention was made that brain acetylcholine is elevated just before and during the time of activity, and reduced during sleep and that acetylcholinesterase activity, which keeps synaptic acetylcholine low, peaks during the subjective night, and is lowest during activity periods (citing Kametani, 1991; Mizuno, 1991; and Schiebeler, 1974). Applicants also acknowledge that it was known to those skilled in the art that systemic administration of the acetylcholinesterase inhibitors phosstigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low disturb sleep and produce awakenings (citing Sitaram, 1979 and Reimann, 1994). Thus, there is clear and unequivocal motivation in the art to formulate acetylcholinesterase inhibitors in compositions that would delay the release of drug until after awakening so as not to disturb sleep and/or interrupt slow wave sleep.

Response to Arguments

The Examiner has added the Davis reference to the above rejections as providing evidence that acetylcholine levels in the brain are known to be higher in animals that are awake than those that are sleeping and that chemicals that that interfere with cholinesterase mechanisms are known to promote REM sleep over slow wave sleep (col. 1, lines 10-22). To the extent that Applicant's arguments pertain to the new rejections set forth above, the Examiner will respond to Applicant's traversal.

Firstly, Applicant argues that cholinesterase inhibitors were not considered psychotropic drugs by Conte. In response, the Examiner respectfully submits that this is an unsupported allegation without factual support. Applicant can not say with certainty what drugs were or were not considered psychotropic drugs by Conte and Applicant has presented no factual evidence to support the allegation that cholinesterase inhibitors are not reasonably psychotropic drugs as disclosed in Conte.

Secondly, Applicant argues that nothing in Conte points towards formulating any drug to delay its release for the purpose of avoiding activity at a particular time rather than promoting activity at a desired time. In response, the Examiner respectfully submits that avoiding activity at a particular time and promoting activity at a desired time are the same thing. If one administers a delayed release formulation as suggested and motivated by Conte, activity of the drug is necessarily delayed until a particular time when the activity, via drug release, is then necessarily promoted.

Thirdly, Applicant argues that the Examiner's statement that one skilled in the art would recognize that a patient with Alzheimer's disease would not be in need of medication while sleeping is "clearly wrong". In support of this argument, Applicant relies on teachings in the art that the most commonly used drug for treatment of Alzheimer's disease continues to be administered in formulations that are active during sleep and at the time of the present invention, the general consensus was that one should not vary the dosage level of Alzheimer's drugs between day and night. However, as evidenced by Davis, acetylcholine levels in the brain are known to be higher in animals that are awake than those that are sleeping and that chemicals that that interfere with cholinesterase mechanisms are known to promote REM sleep over slow wave

sleep. Thus, one skilled in the art would clearly recognize the benefit of not inhibiting acetylcholinesterase with acetylcholinesterase inhibitors during the sleep, when acetylcholine levels are low and inhibition of acetylcholinesterase would disturb slow wave sleep.

Fourthly, with regard to Reimann, Applicant argues that Reimann would not have led one skilled in the art to seek to avoid acetylcholinesterase inhibition during sleep because Reimann teaches that galanthamine administered one hour before bedtime produces awakenings and disturbs sleep only during the first cycle of sleep stages, but not the second or third. However, the Examiner respectfully submits that when taken in conjunction with other cited references, one skilled in the art would have been motivated to formulate acetylcholinesterase inhibitors in compositions that do not release the inhibitors in times of sleep, when acetylcholine levels are low and inhibition of acetylcholinesterase would be expected to reduce slow wave sleep. As Applicant states, the galanthamine preparation which was available at the time of the Reimann study, an immediate-release formulation, "would disturb sleep if given near bedtime" (Response at page 16). While it is certainly true delivering the daily galanthamine dosage at a constant level over the course of a day would avoid the peaks of immediate release galanthamine, a delayed-release galanthamine formulation as suggested and motivated by the cited prior art, given before bedtime, would have the benefit of providing the acetylcholinesterase inhibitor in the morning when acetylcholinesterase activity begins to rise as well as aiding in patient compliance because a patient would not have to remember to take their pill in the morning when they wake.

In summary, Applicant discloses that it was known to those skilled in the art that brain acetylcholine is elevated just before and during the time of activity, and reduced during sleep and that acetylcholinesterase activity, which keeps synaptic acetylcholine low, peaks during the subjective night, and is lowest during activity periods (citing Kametani, 1991; Mizuno, 1991; and Schiebeler, 1974). Applicants also acknowledge that it was known to those skilled in the art that systemic administration of the acetylcholinesterase inhibitors phostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low disturb sleep and produce awakenings (citing Sitaram, 1979 and Reimann, 1994). As such, one skilled in the art would clearly recognize the benefit of delayed release of an acetylcholinesterase inhibitor taking before bedtime. The fact that 24-hour versus daytime treatment of Alzheimer's disease might be

"preferred" does not negate the obvious benefit that would be expected from the dosage forms suggested by the cited prior art.

Accordingly, the rejections are deemed proper and are maintained for the reasons of record and as reiterated above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614